Copy of # 15, 16

HUMAN GENOME SCIENCES
LEGAL DEPARTMENT

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FAX COVER SHEET

DATE: October 15, 2002 TOTAL NUMBER OF PAGES: **33**

TO: U.S. Patent and Trademark Office
Examiner Lorraine Spector (Group Art Unit 1647)

FAX #: (703) 746-5228

FROM: Mark J. Hyman

DIRECT PHONE NO.: **240-314-1224**

RE: **Application Serial No. 09/325,019**
For: Polynucleotides Encoding Connective Tissue Growth Factor-4 (as amended)
Inventor: Young et al.
Our Ref.: PF467

Attached is a copy of Applicants Response and Amendment which was timely filed on April 5, 2002, together with a copy of the date stamped Return Receipt postcard.

RETURN RECEIPT CARD
(MPEP § 503)

OIPE:	Please Date Stamp In The Box Below And Return To Addressee

Application of: Young et al. Attorney Docket No.: PF467

Application Serial No.: 09/325,019 Art Unit: 1647

Filed: June 3, 1999 Examiner: Spector, L.

Title: Polynucleotides Encoding Connective Tissue Growth Factor-4 (as amended)

The following documents were filed by Human Genome Sciences, Inc. via hand delivery on April 5, 2002:

1. Return Receipt Card
2. Fee Transmittal with appropriate fee (in duplicate)
3. Petition for Extension of Time (2 months, to and including April 8, 2002 (April 7, 2002 being a Sunday))
4. Response and Amendment Under 37 C.F.R. § 1.111
5. Version With Markings to Show Changes Made
6. Supplemental Information Disclosure Statement with Form PTO/SB/08 and copies of references AK-AW

MMW/MJH/MMJ/ba

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Application of: Young et al. Attorney Docket No.: PF467

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MMW/MJH/MMJ/ba

PTO/SB/17 (11-01)
Approved for use through 10/31/2002 OMB 0651-0032
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision

☐ Applicant claims small entity status See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 940.00

Complete if Known	
Application Number	09/325,019
Filing Date	June 3, 1999
First Named Inventor	Paul E. Young
Examiner Name	Spector, L.
Group Art Unit	1647
Attorney Docket No	PF467

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account

Deposit Account Number: 08-3425

Deposit Account Name: Human Genome Sciences, Inc

The Commissioner is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) during the pendency of this application

☐ Charge fee(s) indicated below except for the filing fee

to the above-identified deposit account

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims	109	-20** =	20	x	18.00	=	360.00
Independent Claims	6	-3** =	0	x		=	0.00
Multiple Dependent						=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 360.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge – late filing fee or oath	
127	50	227	25	Surcharge – late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for ex parte reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	400.00
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive – unavoidable	
141	1,280	241	640	Petition to revive – unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR 1.17(q)	
126	180	126	180	Submission of Information Disclosure Stmt	180.00
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($) 580.00

SUBMITTED BY

					Complete (if applicable)
Name (Print/Type)	Mark J. Hyman	Registration No (Attorney/Agent)	46,789	Telephone	(240) 314-1224
Signature				Date	April 5, 2002

VIA HAND DELIVERY APRIL 5, 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Young et al. Attorney Docket No : PF467

Application Serial No.: 09/325,019 Art Unit. 1647

Filed: June 3, 1999 Examiner: Spector, L.

Title: Polynucleotides Encoding Connective Tissue Growth Factor-4 (as amended)

PETITION FOR EXTENSION OF TIME UNDER 37 C.F.R. §1.136(a)

Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants petition the Commissioner for Patents to extend the time for response to the Office Action mailed November 7, 2001, for two months from February 7, 2002, to and including April 8, 2002 (April 7, 2002 being a Sunday). Please charge our Deposit Account No. 08-3425 in the amount of $400.00 to cover the cost of the extension, as itemized on the enclosed Fee Transmittal Sheet.

The Commissioner is also authorized to charge any additional required fee or credit any overpayment in connection with this submission to our Deposit Account No. 08-3425.

Respectfully submitted,

Dated: April 5, 2002

Mark J. Hyman Reg. No. 46,789
Attorney for Applicants

Human Genome Sciences, Inc.
9410 Key West Avenue
Rockville, MD 20850
Telephone: (240) 314-1224

MMW/MJH/MMJ/ba

VIA HAND DELIVERY APRIL 5, 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Young et al.	Attorney Docket No.: PF467
Application Serial No.: 09/325,019	Art Unit: 1647
Filed: June 3, 1999	Examiner: Spector, L.

Title: Polynucleotides Encoding Connective Tissue Growth Factor-4 (as amended)

RESPONSE AND AMENDMENT UNDER 37 C.F.R. § 1.111

Commissioner for Patents
Washington, D C. 20231

Sir:

In response to the Office Action mailed November 7, 2001 (Paper No. 14), please consider the following amendments and remarks. Applicants submit concurrently herewith. (a) a Fee Transmittal Sheet with appropriate fee (in dupl.); (b) a Petition for an Extension of Time for a period of time of two months up to and including April 8, 2002 (April 7, 2002 being a Sunday); (c) a Version With Markings To Show Changes Made; and (d) an Information Disclosure Statement, attaching Form PTO/SB/08 and copies of references AK-AW.

Please amend the application as follows:

In the Specification:

Please replace the title of the invention with the following rewritten title:

Polynucleotides Encoding Connective Tissue Growth Factor 4

In the Claims:

Please cancel claims 11, 13, 17-18, 20, 22-23, 25-33, 47-50, and 52-54 without prejudice or disclaimer.

Please amend claims 24, 36, 46, 51, and 57 as follows, without prejudice or disclaimer.

24 (Once amended) An isolated nucleic acid molecule comprising a polynucleotide encoding amino acid residues 1 to 335 of SEQ ID NO:2.

36. (Once amended) The isolated nucleic acid molecule of claim 35 wherein the heterologous polypeptide is the Fc domain of an immunoglobulin.

46. (Once amended) An isolated nucleic acid molecule comprising a first polynucleotide 90% or more identical to a second polynucleotide encoding amino acid residues 1 to 335 of SEQ ID NO:2.

51. (Once amended) The isolated nucleic acid molecule of claim 46 wherein said first polynucleotide is 95% or more identical to said second polynucleotide.

57. (Once amended) The isolated nucleic acid molecule of claim 56 wherein the heterologous polypeptide is the Fc domain of an immunoglobulin.

Please add new claims 106-148 as follows:

106. (New) An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:

(a) a polynucleotide encoding amino acid residues 15 to 84 of SEQ ID NO:2;

(b) a polynucleotide encoding amino acid residues 89 to 154 of SEQ ID NO:2;

(c) a polynucleotide encoding amino acid residues 184 to 228 of SEQ ID NO:2;

(d) a polynucleotide encoding amino acid residues 241 to 316 of SEQ ID NO:2;

(e) a polynucleotide encoding amino acid residues 39 to 55 of SEQ ID NO:2;

(f) a polynucleotide encoding amino acid residues 101 to 121 of SEQ ID NO.2,

(g) a polynucleotide encoding amino acid residues 194 to 213 of SEQ ID NO:2;

(h) a polynucleotide encoding amino acid residues 264 to 280 of SEQ ID NO:2;

(i) a polynucleotide encoding amino acid residues 241 to 335 of SEQ ID NO:2;

(j) a polynucleotide complementary to any polynucleotide (a) through (i), above; and

(k) a polynucleotide complementary to a polynucleotide encoding amino acid residues 1 to 335 of SEQ ID NO:2

107 (New) The isolated nucleic acid molecule of claim 106, wherein said polynucleotide is (a).

108. (New) The isolated nucleic acid molecule of claim 106, wherein said polynucleotide is (b).

109. (New) The isolated nucleic acid molecule of claim 106, wherein said polynucleotide is (c).

110. (New) The isolated nucleic acid molecule of claim 106, wherein said polynucleotide is (d).

111. (New) The isolated nucleic acid molecule of claim 106, wherein said polynucleotide is (e).

112. (New) The isolated nucleic acid molecule of claim 106, wherein said polynucleotide is (f).

113. (New) The isolated nucleic acid molecule of claim 106, wherein said polynucleotide is (g).

114. (New) The isolated nucleic acid molecule of claim 106, wherein said polynucleotide is (h).

115. (New) The isolated nucleic acid molecule of claim 106, wherein said polynucleotide is (i).

116. (New) The isolated nucleic acid molecule of claim 106, wherein said polynucleotide is (j).

117 (New) The isolated nucleic acid molecule of claim 106, wherein said polynucleotide is (k).

118. (New) The isolated nucleic acid molecule of claim 106 wherein the polynucleotide further comprises a heterologous polynucleotide.

119. (New) The isolated nucleic acid molecule of claim 107 wherein said heterologous polynucleotide encodes a heterologous polypeptide.

120. (New) The isolated nucleic acid molecule of claim 108 wherein the heterologous polypeptide is the Fc domain of an immunoglobulin.

121. (New) A recombinant vector comprising the isolated nucleic acid molecule of claim 106.

122. (New) The recombinant vector of claim 110 wherein the nucleic acid molecule is operably associated with a heterologous regulatory sequence that controls gene expression.

123. (New) A method of producing a recombinant vector comprising inserting the isolated nucleic acid molecule of claim 106 into a vector.

124. (New) A recombinant host cell comprising the isolated nucleic acid molecule of claim 106.

125. (New) The recombinant host cell of claim 113 wherein the nucleic acid molecule is operably associated with a heterologous regulatory sequence that controls gene expression.

126. (New) A recombinant host cell comprising the recombinant vector of claim 110.

127. (New) A method of producing a host cell comprising transducing, transforming or transfecting a host cell with the vector of claim 110.

128. (New) A method for producing a protein, comprising:

(a) culturing the host cell of claim 113 under conditions suitable to produce a polypeptide encoded by the nucleic acid molecule; and

(b) recovering the protein from the cell culture.

129. (New) A composition comprising the polynucleotide of claim 106 and a pharmaceutically acceptable carrier

130. (New) An isolated nucleic acid molecule comprising a first polynucleotide 90% or more identical to a second polynucleotide selected from the group consisting of:

(a) a polynucleotide encoding amino acid residues 15 to 84 of SEQ ID NO:2;

(b) a polynucleotide encoding amino acid residues 89 to 154 of SEQ ID NO:2; and

(c) a polynucleotide encoding amino acid residues 241 to 335 of SEQ ID NO:2

131. (New) The isolated nucleic acid molecule of claim 130, wherein said second polynucleotide is (a).

132. (New) The isolated nucleic acid molecule of claim 130, wherein said second polynucleotide is (b).

133. (New) The isolated nucleic acid molecule of claim 130, wherein said second polynucleotide is (c).

134. (New) The isolated nucleic acid molecule of claim 130, wherein said first polynucleotide is 95% or more identical to said second polynucleotide (a).

135. (New) The isolated nucleic acid molecule of claim 130, wherein said first polynucleotide is 95% or more identical to said second polynucleotide (b).

136. (New) The isolated nucleic acid molecule of claim 130, wherein said first polynucleotide is 95% or more identical to said second polynucleotide (c).

137. (New) The isolated nucleic acid molecule of claim 130 wherein the isolated nucleic acid molecule further comprises a heterologous polynucleotide

138. (New) The isolated nucleic acid molecule of claim 137 wherein said heterologous polynucleotide encodes a heterologous polypeptide.

139. (New) The isolated nucleic acid molecule of claim 138 wherein the heterologous polypeptide is the Fc domain of an immunoglobulin.

140. (New) A recombinant vector comprising the isolated nucleic acid molecule of claim 130.

141 (New) The recombinant vector of claim 140 wherein the nucleic acid molecule is operably associated with a heterologous regulatory sequence that controls gene expression.

142. (New) A method of producing a recombinant vector comprising inserting the isolated nucleic acid molecule of claim 130 into a vector

143. (New) A recombinant host cell comprising the isolated nucleic acid molecule of claim 130.

144. (New) The recombinant host cell of claim 143 wherein the nucleic acid molecule is operably associated with a heterologous regulatory sequence that controls gene expression.

145. (New) A recombinant host cell comprising the recombinant vector of claim 140.

146. (New) A method of producing a host cell comprising transducing, transforming or transfecting a host cell with the vector of claim 140.

147. (New) A method for producing a protein, comprising:

(a) culturing the host cell of claim 143 under conditions suitable to

produce a polypeptide encoded by the nucleic acid molecule, and

(b) recovering the protein from the cell culture.

148. (New) A composition comprising the polynucleotide of claim 130 and a pharmaceutically acceptable carrier.

Remarks

Applicants have canceled claims 11, 13, 17-18, 20, 22-23, 25-33, 47-50, and 52-54 without prejudice or disclaimer. Applicants have also amended claims 24 and 46 without prejudice or disclaimer to cancel sub-parts 24(b)-(k) and 46(b)-(d); Applicants have added new claims 106-148 to correspond to the subject matter of claims 24(b)-(k) and 46(b)-(d). Further, claims 36 and 57 have been amended to insert the article "an" prior to "immunoglobulin," and claim 51 has been amended to remove the phrase "further comprises," both without prejudice or disclaimer. Attached hereto is a marked-up version of the changes made by the current amendments, captioned "Version With Markings To Show Changes Made." The amendments are fully supported by the specification and claims as originally filed, and thus no new matter has been added.

Claims 24, 34-46, 51, and 55-148 will be pending upon entry of these amendments.

I. Objection to the Title

The Examiner has objected to the title because it allegedly is not descriptive. *See* Paper No. 14, page 4, lines 20-21.

In response, Applicants have amended the title to more clearly indicate that the instant claims are directed to "Polynucleotides Encoding Connective Tissue Growth Factor 4." Applicants submit that this amendment addresses the Examiner's objection, and that the title as amended fully complies with 37 C.F.R. § 1.72(a). Accordingly, it is respectfully requested that the Examiner's objection to the title be reconsidered and withdrawn.

II. Objection to the Claims

The Examiner has objected to the claims as allegedly encompassing multiple patentably distinct inventions, and has required amendment of the claims to include only the elected invention. *See* Paper No. 14, page 4, lines 23-25.

Applicants preliminarily note that the restriction requirements in Paper Nos. 6 and 10 have been traversed in Applicants' responses of January 25, 2001 and August 15, 2001, respectively; the Examiner acknowledged such traversals in Paper Nos. 10 and 14, respectively. Thus, Applicants retain the right to petition from the restriction requirements under 37 C.F.R. § 1.144.

However, Applicants have amended the claims that included non-elected inventions, as required by the Examiner. In particular, Applicants have amended claim 24 to include only former sub-part (a); new claims 106-129, directed to former sub-parts (b)-(k), have been added to retain the non-elected subject matter removed from claim 24. Likewise, Applicants have amended claim 46 to include only former sub-part (a); new claims 130-148, directed to former sub-parts (b)-(d), have been added to retain the non-elected subject matter removed from claim 46.

Applicants submit that these amendments fully address the Examiner's objection to the claims. Accordingly, it is respectfully requested that the Examiner's objection to the claims be reconsidered and withdrawn.

III. Non-Consideration of References AE-AI

The Examiner has indicated that References AE-AI, submitted with the Information Disclosure Statement filed January 25, 2001, have not been considered, as

they are allegedly "merely sequences with no explanation of relevance or alignment with the disclosed sequences, such that relevancy to the claimed invention cannot be assessed." Paper No. 14, page 5, lines 1-3.

In response, Applicants respectfully note that neither 37 C.F.R. § 1.97 or § 1.98 provide that failure to provide an explanation of relevance or an alignment for sequence information cited in an Information Disclosure Statement is a proper basis for failing to consider such information. *See also* M.P.E.P. § 609(III). Accordingly, Applicants respectfully submit that References AE-AI were properly submitted and should have been considered by the Examiner

However, as an explanation of the relevancy of References AE-AI, Applicants point out that the references were cited as category X/Y documents by Examiner Spector in the International Search Report (Reference AS submitted herewith) for International Application PCT/US99/12150, which is a counterpart international application of the instant U.S. application. *See* 37 C.F.R. § 1.56(a)(2). As a courtesy to the Examiner, References AE-AI have again been cited on the Information Disclosure Statement enclosed herewith; a copy of each reference is also enclosed

Accordingly, Applicants respectfully ask that the Examiner consider References AE-AI, and return an initialed copy of Form PTO/SB/08 with the next Office Action.

IV. Rejections Under 35 U.S.C. §§ 101 and 112, First Paragraph

The Examiner has rejected claims 24, 25, 34-47, 51, and 55-66 under 35 U.S.C. § 101 because the invention is allegedly not supported by either a credible, specific,

substantial asserted utility or a well established utility. *See* Paper No. 14, pages 5-8. In particular, the Examiner contends that:

> The assertion that the disclosed CTGF-4 would have biological activities similar to known HBGF cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities.

The Examiner has further rejected claims 24, 25, 34-47, 51, and 55-66 under 35 U.S.C. § 112, first paragraph, because one skilled in the art would allegedly not know how to use the claimed invention, based on the supposed lack of either a credible, specific, substantial asserted utility or a well established utility. *See id.*, page 8.

Applicants respectfully disagree and traverse these rejections.

Preliminarily, Applicants note that the Examiner has acknowledged that the specification asserts utilities for CTGF-4 (Paper No. 14, page 5, lines 20-23, page 6, lines 7-8, and page 7, lines 5-6). In particular, the specification teaches the use of the claimed invention in diagnostic methods for detecting disorders related to connective tissue, such as cancer, as well as the use of the claimed invention in the treatment of cancer. *See, e.g.*, Specification at pages 1, 73-75, and 125-126.

It is well established that "[a]n applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C 101." M.P.E.P. § 2107.02(III)(A) at 2100-39; *see also In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974) Thus, the burden is on the Examiner to establish that it is more likely than not that a person of ordinary skill in the art would not consider the utility asserted by Applicants to be specific, substantial, and credible. *See* M.P.E.P. § 2107 at 2100-30. Such a *prima facie* showing must contain (1) an explanation that clearly sets

forth the reasoning used in concluding that the asserted utility for the claimed invention is not specific, substantial, and credible; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. *See id.* Moreover, the Examiner must establish why it is more likely than not that one of ordinary skill in the art would doubt (*i.e.*, "question") the truth of the statement of utility. *See id.*; *see also In re Cortright*, 49 U.S.P.Q 2d 1464, 1466 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566, 34 U.S P.Q 2d 1436, 1441 (Fed. Cir. 1995). Indeed, the Utility Guidelines note that:

> Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.
>
> M.P.E.P. § 2107.02 at 2100-40.

For the reasons set forth below, the Examiner has not met this burden, and thus the rejection of the claims for lack of utility under 35 U.S.C. § 101 must be withdrawn.

In particular, the Examiner bases the allegation that the asserted utility is not credible, substantial, and specific on references discussing different proteins that allegedly support the assertion that "[o]ne cannot rely upon structural similarity alone to determine functionality." Applicants respectfully disagree with the Examiner's conclusion, and note that those of skill in the art routinely rely on homology as predictive of protein function. Further, evidence directed to the predictability of function based on proteins distinct from the instant protein, rather than close family members such as CTGF or HBGF, cannot

support the instant rejection. Indeed, M.P.E.P. § 2107 notes that the Examiner should consider "the closest prior art," yet the Examiner has presented no evidence directed to CTGF or HBGF. The Examiner has made no showing, for example, that the asserted utility is inconsistent with the function of other CCN family members, such as connective tissue growth factor [CTGF], Cyr61/Cef10, and neuroblastoma overexpressed gene product [Nov]. Nor has the Examiner identified a reference suggesting that CTGF-4 has activities that do not correlate with the asserted utilities. Thus, the Examiner has not met the required burden to show that Applicants' asserted utility is not credible.

Additionally, Applicants respectfully direct the attention of the Examiner to the post-filing date references Xu et al., Genes & Development, 14: 585-595 (2000), Xie et al., Cancer Research, 61: 8917-8923 (December 2001), Desnoyers et al., The Journal of Biological Chemistry, 276(50): 47599-47607 (December 2001), Su et al., Genes & Development, 16: 46-57 (2002), and Tanaka et al., Oncogene, 20(39): 5525-32 (September 2001) (submitted herewith as references AK-AW with the enclosed Information Disclosure Statement). Xu et al. disclose that WISP-1 (which is identical to CTGF-4) overexpression in rat kidney fibroblast cells (NRK-49F) induced morphological transformation, accelerated cell growth, enhanced saturation density. Moreover, Xu et al. also disclose that subcutaneous injection of WISP-1 into nude mice induced tumor formation. Xie et al. disclose that elevated levels of WISP-1 are found in primary breast cancers. Desnoyers et al. disclose that WISP-1 binding to the stroma of colon tumors and to fibroblast-like cells was modulated by decorin and biglycan. Su et al. disclose that WISP-1 activates the Akt/PKB anti-apoptotic signaling pathway. Tanaka et al. disclose that a variant of WISP-1 was found to be overexpressed in scirrhous gastric carcinoma.

Thus, all the above references suggest that CTGF-4 acts to promote and contribute to tumorigenesis upon binding to cancerous cells or cells with fibroblast phenotype. Because the polynucleotide sequence of WISP-1 is identical at 1003 of 1005 nucleotides over the open reading frame encoded by nucleic acids 3 to 1007 of SEQ ID NO:1, and the polypeptide sequence is identical at 335 of 335 amino acids to the sequence of SEQ ID NO:2, the observations described above support the credibility of Applicants' asserted utility for CTGF-4.

Indeed, the Patent Office has stated that utility can exist for therapeutic inventions "despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition." M.P.E.P. § 2107.01(III). "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) (emphasis added). Indeed, there is no need to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty or provide actual evidence of success in treating humans where such a utility is asserted. *See* M.P.E.P. §§ 2107.01(III) and 2701.03. All that is required of Applicants is that there be a reasonable correlation between the biological activity and the asserted utility, as is clearly present in this case. *See Nelson v Bowler*, 626 F.2d 853, 857 (C.C.P.A. 1980).

Applicants point out that subsequently-generated data (*e.g.*, Xu et al., Xie et al., Desnoyers et al., Su et al., and Tanaka et al.) can be used to support the credibility of a

utility asserted in the specification. As the Federal Circuit held in *In re Bruna*, evidence dated after the filing date "can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification." 51 F. 3d. 1560, 1567 at n.19 (Fed. Cir. 1995). Such evidence "goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." *Id., citing In re Marzocchi*, 439 F2d. at 224 n.4, 169 U.S.P.Q at 370 n.4. Indeed, the Utility Examination Guidelines in the M.P.E.P. specifically contemplate the use of such additional data:

> In such a case, the examiner should challenge the use and require sufficient evidence of operativeness. The purpose of this authority is to enable an applicant to cure an otherwise defective factual basis for the operability of an invention. Because this is a curative authority (e.g., evidence is requested to enable an applicant to support an assertion that is inconsistent with the facts of record in the application), Office personnel should indicate not only why the factual record is defective in relation to the assertions of the applicant, but also, where appropriate, what type of evidentiary showing can be provided by the applicant to remedy the problem.
>
> *See* M.P.E.P. § 2107.02(V) at 2100-41 to 42.

Thus, Applicants have shown that CTGF-4 has biological activities that are reasonably correlated with the asserted utilities, as discussed above. Thus, the only reasonable conclusion that can be reached based on the data and assertions of utility in the specification, supported by Xu et al., Xie et al., Desnoyers et al., Su et al., and Tanaka et al., is that the present invention is useful for the purposes asserted in the specification, namely modulating mitogenic activity of fibroblasts and tumors. Accordingly, even assuming *arguendo* that the Examiner has made a *prima facie* showing that Applicants' asserted utility is not specific, substantial, or credible, Applicants respectfully submit that the *prima facie* showing has been rebutted, and that the presently claimed invention possesses specific, substantial, and credible utilities which constitute patentable utilities

under 35 U S C. § 101. In view of the above, Applicants respectfully request that the Examiner's prior rejection of the claims under 35 U.S.C. § 101 be reconsidered and withdrawn.

Further, the Federal Circuit and its predecessor determined that the utility requirement of 35 U.S.C. § 101 and the how to use requirement of 35 U.S.C. § 112, first paragraph, have the same basis, *i e.*, the disclosure of a credible utility *See In re Brana*, 51 F.3d 1560, 1564, 34 U.S P.Q.2d 1436, 1441 (Fed. Cir. 1995); *see also* M.P.E.P. § 2107(IV). As discussed above, the specification teaches specific and well-established utilities of the claimed invention, thereby enabling the skilled artisan to use the claimed polynucleotides. Since the specification teaches how to use the claimed polynucleotides with only routine experimentation and the specification describes specific and immediate utilities for the claimed invention, Applicants submit that the full scope of the claims is enabled. Accordingly, it is respectfully requested that the Examiner's rejection of the claims under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

V. Rejections of the Claims Under 35 U.S.C. § 112, Second Paragraph

A. Claims 34-36 and 55-57

The Examiner has rejected claims 34-36 and 55-57 under 35 U.S.C. § 112, second paragraph as being "indefinite for failing to indicate the relationship between the recited structural elements". *See* Paper No. 14, page 8, lines 27-28 In particular, the Examiner alleges that:

> In claim 34, it is not clear whether the "heterologous sequence" is attached at an end or might be internally inserted In claims 35 and 36, it is not clear whether applicants intend an operable attachment that would produce a

> fusion protein, or merely that the two recited portions be present on the same vector. Claims 55-57 are similarly indefinite.
>
> Paper No. 14, page 8, line 29 to page 9, line 4.

In response, Applicants respectfully disagree and traverse. While claims 34 and 55 encompass polynucleotides (of claim 24 or 46, respectively) with a heterologous polynucleotide attached at an end or internally inserted, merely because the claims encompass both relationships does not render them indefinite. Likewise, although claims 35 and 56 encompass heterologous polynucleotides that are operably attached to the instant polynucleotides to produce a fusion protein, or without such an operable attachment (*e g*, as a selectable marker on a vector), the claims are not indefinite. The breadth of a claim is not to be equated with indefiniteness *See* M.P.E.P § 2173.04; *In re Miller*, 441 F.2d 689, 169 U.S.P.Q 597 (C.C.P.A. 1971). Applicants should not be required to present separate claims, since one of skill in the art would recognize (as the Examiner did) that claims encompass both embodiments. Thus, since claims 34-35 and 55-56 have been set forth with "a reasonable degree of particularity and distinctness," 35 U S.C. § 112, second paragraph has been fully complied with. *See* M.P.E.P. § 2173.02. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the instant rejection.

With respect to claims 36 and 57, the Examiner contends that it is unclear as to which immunoglobulin the claims refer, and suggests the insertion of the article "an" prior to the term "immunoglobulin" to overcome the instant rejection. In response, while Applicants disagree and assert that the claims fully comply with 35 U.S.C. § 112, second paragraph, claims 36 and 57 have been amended as requested by the Examiner. Accordingly, Applicants submit that the Examiner's rejection of claims 36 and 57 under

35 U.S C. § 112, second paragraph has been obviated, and respectfully request that the rejection be reconsidered and withdrawn.

B. The Term "Further Comprises"

The Examiner has rejected claims 47 and 51 under 35 U.S C. § 112, second paragraph as being indefinite for reciting the term "further comprises" See Paper No. 14, page 9

In response, while Applicants disagree with the instant rejection, Applicants note that claim 47 has been canceled, and claim 51 has been amended without prejudice or disclaimer to remove the language objected to by the Examiner Accordingly, the instant rejection has been obviated, and Applicants respectfully request that the rejection of claims 47 and 51 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

Conclusion

Entry of the above amendment is respectfully solicited. In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for in the Petition for an Extension of Time

submitted concurrently herewith, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Respectfully submitted,

Dated: April 5, 2002

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MMW/MJH/MMJ/ba

VIA HAND DELIVERY APRIL 5, 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Young et al. Attorney Docket No.. PF467

Application Serial No.: 09/325,019 Art Unit: 1647

Filed: June 3, 1999 Examiner: Spector, L.

Title: Polynucleotides Encoding Connective Tissue Growth Factor-4 (as amended)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 24, 36, 46, 51, and 57 have been amended as follows, without prejudice or disclaimer:

24. (Once amended) An isolated nucleic acid molecule comprising a polynucleotide ~~selected from the group consisting of:~~

~~(a) a polynucleotide~~ encoding amino acid residues 1 to 335 of SEQ ID NO:2~~;~~

~~(b) a polynucleotide encoding amino acid residues 15 to 81 of SEQ ID NO:2;~~

~~(c) a polynucleotide encoding amino acid residues 89 to 151 of SEQ ID NO:2;~~

~~(d) a polynucleotide encoding amino acid residues 184 to 228 of SEQ ID NO:2;~~

~~(e) a polynucleotide encoding amino acid residues 241 to 316 of SEQ ID NO:2;~~

~~(f) a polynucleotide encoding amino acid residues 39 to 55 of SEQ ID NO:2;~~

~~(g) a polynucleotide encoding amino acid residues 101 to 121 of SEQ ID NO:2,~~

~~(h) a polynucleotide encoding amino acid residues 194 to 213 of SEQ ID NO:2;~~

~~(i) a polynucleotide encoding amino acid residues 264 to 280 of SEQ ID NO:2;~~

~~(j) a polynucleotide encoding amino acid residues 241 to 335 of SEQ ID NO:2; and~~

~~(k) a polynucleotide complementary to any polynucleotide (a) through (j), above.~~

36. (Once amended) The isolated nucleic acid molecule of claim 35 wherein the heterologous polypeptide is the Fc domain of an immunoglobulin.

46. (Once amended) An isolated nucleic acid molecule comprising a first polynucleotide 90% or more identical to a second polynucleotide ~~selected from the group consisting of:~~

~~(a) a polynucleotide~~ encoding amino acid residues 1 to 335 of SEQ ID NO.2,

~~(b) a polynucleotide encoding amino acid residues 15 to 84 of SEQ ID NO:2;~~

~~(c) a polynucleotide encoding amino acid residues 89 to 154 of SEQ ID NO:2, and~~

~~(d) a polynucleotide encoding amino acid residues 241 to 335 of SEQ ID NO:2~~.

51 (Once amended) The isolated nucleic acid molecule of claim 46 wherein said ~~which further comprises a~~ first polynucleotide is 95% or more identical to ~~a~~ said second polynucleotide ~~encoding amino acid residues 1 to 335 of SEQ ID NO:2~~.

57. (Once amended) The isolated nucleic acid molecule of claim 56 wherein the heterologous polypeptide is the Fc domain of an immunoglobulin.

VIA HAND DELIVERY APRIL 5, 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Young et al. Attorney Docket No.: PF467

Application Serial No.: 09/325,019 Art Unit: 1647

Filed: June 3, 1999 Examiner: Spector, L.

Title: Polynucleotides Encoding Connective Tissue Growth Factor-4 (as amended)

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. § 1.97

Commissioner for Patents
Washington, D.C. 20231

Sir:

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 to inform the Patent and Trademark Office of all references coming to the attention of each individual associated with the filing or prosecution of the subject application, which are or may be material to the patentability of a claim of the subject application, Attorney for Applicants hereby directs the Examiner's attention to references AE-AW listed on the attached revised Form PTO/SB/08. Copies of the references are enclosed.

The listed references are presented so that the Patent and Trademark Office can determine any materiality thereof to the claimed invention. See 37 C.F.R. § 1.104(a) concerning the Examiner's duty to consider and use any such information. Applicants respectfully request that the Examiner make the listed references of record in the file history of the application, and consider the information contained therein during the prosecution of this application.

Identification of the listed references is not to be construed an admission of any individual associated with the filing or prosecution of the subject application that such references are available as "prior art" against the subject application. Furthermore, Applicants do not waive any rights to take appropriate action to establish patentability over any of the listed documents should they be applied as references against the claims of the subject application.

Pursuant to 37 C.F.R. § 1.97(c), since this Supplemental Information Disclosure Statement is being filed after the mailing date of a first Office Action on the merits and before either a final action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311, or an action that otherwise closes prosecution, the Patent and Trademark Office will consider this Supplemental Information Disclosure Statement if it is accompanied by the fee as specified in 37 C.F.R. § 1.17(p).

Accordingly, the Patent Office is hereby authorized to charge our Deposit Account No. 08-3425 in the amount of $180.00 as payment of the fee required under 37 C.F.R. § 1.17(p), as itemized on the enclosed Fee Transmittal Sheet. The Patent Office is also authorized to charge any additional required fee or credit any overpayment in connection with this submission to our Deposit Account No. 08-3425.

Respectfully submitted,

Dated. April 5, 2002

Mark J. Hyman Reg. No. 46,789
Attorney for Applicants

Human Genome Sciences, Inc.
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Rockville, MD 20850
Telephone: (240) 314-1224

MMW/MJH/MMJ/ba

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	09/325,019
Filing Date	June 3, 1999
First Named Inventor	Young et al.
Group Art Unit	1647
Examiner Name	Spector, L
Attorney Docket Number	PF467

OTHER REFERENCES - NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
	AE	GenBank Accession No. AI683855, "tx77h09.x1 NCI_CGAP_Ut1 Homo sapiens cDNA clone IMAGE:2275649 3'," May 26, 1999	
	AF	GenBank Accession No. AI372973, "qz17f11.x1 NCI_CGAP_CLL1 Homo sapiens cDNA clone IMAGE.2021805 3' similar to contains element L1 repetitive element ," January 12, 1999	
	AG	GenBank Accession No. T55016, "yb42e03.r1 Stratagene fetal spleen (#937205) Homo sapiens cDNA clone IMAGE.73852 5'," February 6, 1995	
	AH	GenBank Accession No. AA316760, "EST18843 Lung Homo sapiens cDNA 5' end," April 19, 1997	
	AI	GenBank Accession No. AA393740, "zv64b08.r1 Soares_total_fetus_Nb2HF8_9w Homo sapiens cDNA clone IMAGE 758391 5'," April 24, 1997.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet	2	of	2

Complete if Known	
Application Number	09/325,019
Filing Date	June 3, 1999
First Named Inventor	Young et al.
Group Art Unit	1647
Examiner Name	Spector, L.
Attorney Docket Number	PF467

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Document: Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AK	5,585,270	B1	Grotendorst et al.	12-17-1996	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Office[3]	Number[4]	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[5]
	AL	WO	00/73348	A2	Genentech, Inc.	12-07-2000		
	AM	WO	01/53486	A1	Genentech, Inc	07-26-2001		

OTHER REFERENCES - NON PATENT LITERATURE DOCUMENTS

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	AN	XIE et al., "Elevated Levels of Connective Tissue Growth Factor, WISP-1, and CYR61 in Primary Breast Cancers Associated with More Advanced Features," *Cancer Research*, 61:8917-8923 (December 15, 2001)	
	AO	SU et al., "WISP-1 attenuates p53-mediated apoptosis in response to DNA damage through activation of the Akt kinase," *Genes & Development*, 16:46-57 (2002)	
	AP	DESNOYERS, et al., "WISP-1 Binds to Decorin and Biglycan," *J Biol Chem*, 276(50):47599-47607 (December 14, 2001)	
	AQ	XU et al., "WISP-1 is a Wnt-1- and β-catenin-responsive oncogene," *Genes & Development*, 14:585-595 (2000).	
	AR	TANAKA et al., "A novel variant of *WISP1* lacking a Von Willebrand type C module overexpressed in scirrhous gastric carcinoma," *Oncogene*, 20:5525-5532 (2001)	
	AS	INTERNATIONAL SEARCH REPORT, International Application No. PCT/US99/12150, mailed October 22, 1999	

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